UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,503	11/17/2006	Rasappa G. Arumugham	15270C-000110US	4013

20350 7590 05/19/2010

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
GUDIBANDE, SATYANARAYAN R	
ART UNIT	**PAPER NUMBER**
1654	

MAIL DATE	DELIVERY MODE
05/19/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,503	ARUMUGHAM ET AL.	
	Examiner	Art Unit	
	SATYANARAYANA R. GUDIBANDE	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *380-423* is/are pending in the application.

4a) Of the above claim(s) *380-397,403,409,415 and 417-423* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *398-402,404-408,410-414 and 416* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/20/2008,03/05/2009,04/13/2009,10/30/2009, 01/25/2010*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group XLV directed to conjugates and immunogenic compositions comprising CRM_{197} as the carrier protein, SEQ ID NO: 2 as the species of Aβ peptide, N-succinimidyl bromoacetate as the species of the cross-linking reagent and N-acetylcysteamine as the capping reagent in the reply filed on 3/5/09 is acknowledged. The traversal is on the ground(s) that the citation that has been used by the office to establish 'lack of unity' does not show the special technical feature of capping of unreacted derivatized functional groups on the conjugate that prevents it from engaging in further reaction. This is not found persuasive because though, Shimizu does not explicitly fails to provide evidence of such capping step, the method of such capping step is routinely used in the labeling and conjugation reaction, for example, Brinkley, 1992, Bioconjugate chemistry, 3, 2-13 describes general methods for protein labeling and for preparing conjugates with haptens using variety of cross linking agents. Brinkley also discloses that "upon completion of the reaction with the protein, an excess of glutathione, mercaptoethanol or other small molecular weight thiol can be added to consume excess of modification reagent thus ensuring no reactive species are present during purification step" (page 10, column 2, paragraph 3). This clearly illustrates that capping of reactive species, in this case thiol cross-linking agents are inactivated or capped off using simple thiols or glutathione.

Hence the requirement is still deemed proper and is therefore made FINAL.

Status of pending claims

Claims 380-423 are pending.

Claims 380-397 and 417-423 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/5/09.

Claims 403, 409 and 415 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/5/09.

Claims 398-402, 404-408, 410-414 and 416 are examined on the merit.

A search for the elected species of the peptide SEQ ID NO: 2 indicated that it is not free of prior art. The art found has been applied in the rejection set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 398-402, 404-408, 410-414 and 416 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 398 and 404 recite 'analogs of Aβ peptide'. The instant specification does not provide a limiting definition for the term 'analog'. The definition provided in the specification is "[A]nalogs including allelic, species and induced variants. Analogs typically differ from harm-ally occurring peptides at one, two or a few positions, often by virtue of conservative

substitutions. Analogs typically exhibit at least 80 or 90% sequence identity with natural peptides. Some analogs also include unnatural amino acids or modifications of N- or C-terminal amino acids at one, two, or a few positions. For example, the natural aspartic acid residue at position 1 and/or 7 or Aβ can be replaced with iso-aspartic acid". Hence, it is unclear form the claim as recited and the definition as provided in the specification the true chemical nature of these Aβ peptide analogs. According to the definition for 'analog' provided by International Union of Pure and Applied Chemistry (IUPAC), in Wermuth, Pure and Appl. Chem, 1998, 70, 1129-1143, "an analog is a drug whose structure is related to that of another drug but whose chemical and biological properties may be quite different" (Page 1131). Therefore, the disclosure of the chemical structure for the analogs that correlates with the desired biological function is essential. Hence the claims are being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 398-402, 404-408, 410-414 and 416 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant invention, applicants claim conjugate comprising a peptide immunogen/polypeptide carrier conjugate wherein the peptide immunogen comprising a Aβ peptide or fragment or analog thereof and wherein the derivatized polypeptide functional group is capped thereby the carrier polypeptide retains the immune response functionality against the peptide conjugate that would otherwise not occur without the carrier. Claims 398 and 404 as presented also recite 'analogs of Aβ peptide'.

Factors to be considered in making the determination as to whether one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing include:

a. Actual reduction to practice;
b. Disclosure of drawings or structural chemical formulas;
c. Sufficient relevant identifying characteristics such as:
    i. Complete structure,
    ii. Partial structure,
    iii. Physical and/or chemical properties or
    iv. Functional characteristics when coupled with a known or disclosed correlation between function and structure;
d. Method of making the claimed invention;
e. Level of skill and knowledge in the art and
f. Predictability in the art.

While all of these factors are considered, a sufficient number for a *prima facie* case are discussed below.

The instant specification does not provide a limiting definition for the term 'analog'. The definition provided in the specification is "[A]nalogs including allelic, species and induced variants. Analogs typically differ from harm-ally occurring peptides at one, two or a few positions, often by virtue of conservative substitutions. Analogs typically exhibit at least 80 or 90% sequence identity with natural peptides. Some analogs also include unnatural amino acids or modifications of N- or C-terminal amino acids at one, two, or a few positions. For example, the natural aspartic acid residue at position 1 and/or 7 or Aβ can be replaced with iso-aspartic acid". Hence, it is uncertain form the claim as recited and the definition as provided in the specification

the true chemical nature of these Aβ peptide analogs. According to the definition for 'analog' provided by International Union of Pure and Applied Chemistry (IUPAC), in Wermuth, Pure and Appl. Chem, 1998, 70, 1129-1143, "an analog is a drug whose structure is related to that of another drug but whose chemical and biological properties may be quite different" (Page 1131).

The lack of a limiting definition for the term 'analog' and applicants have not disclosed any analogs of the peptides in the instant specification. The sequence listing filed in the instant invention does not contain any analogs of Aβ peptide. The specification as disclose does not present any analogs of the Aβ peptide. Hence, the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 398-402, 404-408, 410-414 and 416 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brinkley, 1992, Bioconjugate chemistry, 3, 2-13, in view of Shimizu, Journal of Neuroscience Research, 70, 451-461, in view of Askelof, PNAS, 87, 1347-1351 and further in view of Marburg (US 4,882,317).

In the instant invention, applicants claim conjugate comprising a peptide immunogen/polypeptide carrier conjugate wherein the peptide immunogen comprising a Aβ peptide or fragment or analog thereof and wherein the derivatized polypeptide functional group is capped thereby the carrier polypeptide retains the immune response functionality against the peptide conjugate that would otherwise not occur without the carrier.

Brinkley discloses a protein conjugated to a bifunctional derivatizing agent 'amine reactive iodoacetamide' as illustrated in the reaction scheme (15) (page 6, column 2, paragraph 2) and various other schemes disclosed in Brinkley. Brinkley further discloses that this modified protein can then be coupled to any thiol containing molecule. The second molecule is usually a thiol-containing protein (polypeptide). In the general procedure section for thiol reactive probes on page 10, column 2, paragraphs 1-3, Brinkley further suggests that upon completion of the reaction with the protein an excess of glutathione (an SH-containing peptide) or mercaptoethanol or other soluble low molecular weight thiol can be added to consume the excess modification reagent thus ensuring that no reactive species are present (page 10, column 2, paragraph 3). The method disclosed by Brinkley is for protein conjugates with dyes and haptens and hence useful for immunization (Introduction). This reads on the carrier protein-peptide conjugate of the

instant invention wherein the unreacted derivatized reactive functional groups are capped to reduce the reactive nature of the conjugate as illustrated by Brinkley. This reads on the instant claims 398 and 404.

Though Brinkley teaches the general method of preparing the protein conjugates for immunization, it does not specifically disclose the Aβ peptide or fragments or analogs thereof.

Shimizu discloses the conjugate of KLH with Aβ1-12 peptide that comprises the fragment of instantly elected SEQ ID NO:2 (page 452, column 2). This reads on the instant claims 398, 399, 401, 402, 404, 405, 407 and 408. Since the conjugate of Shimizu were administered to rabbits, it comprises of pharmaceutically acceptable carriers and hence reads on instant claims 411, 413, 414, 415 and 416.

Brinkley discloses the general procedure for preparing the protein-immunogen (hapten) conjugate, Shimizu discloses KLH as the carrier protein for the preparation of the immunogen conjugate. Both Brinkley and Shimizu does not explicitly disclose the elected species of the carrier protein CRM_{197}.

Askelof discloses the peptide-carrier protein conjugate as an immunogen wherein the carrier protein is CRM_{197}. Askelof further discloses that peptide- CRM_{197} induced high antibody titer against the native toxin in mice (Abstract). This reads on the instant claims 399, 400, 405, 406, 411 and 412.

Brinkley discloses glutathione (an SH-containing peptide) or mercaptoethanol or other soluble low molecular weight thiol as capping reagents that can be added to consume the excess modification reagent thus ensuring that no reactive species are present. Brinkley does not exclusively disclose the instantly claimed N-acetylcysteamine.

Marburg discloses that conjugate formed between thiolated protein and the functionalized HIb-polysaccharide with butadiamine-bromoacetate was capped with N-acetylcysteamine (column 26, example 4). This clearly demonstrates that the unreacted reactive functionalized biomolecule be capped (rendered non-reactive) with the capping reagent such as N-acetylcysteamine.

It would have obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Brinkley, Shimizu, Askelof and Marburg to arrive at the instant invention. Brinkley clearly teaches the various steps involved in the carrier protein conjugates with haptens including the capping step to prevent the unreacted reactive functionalized biomolecule. Although, Brinkley does not explicitly discloses the Aβ peptide as the peptide for conjugating to the carrier protein, one of skilled in the art would be motivated utilize the general concepts of Brinkley with the disclosure Shimizu to use the Aβ peptide as the hapten and CRM_{197} as the carrier protein as they have been disclosed by Shimizu and Askelof. One of ordinary skill in the art would be motivated to use the N-acetylcysteamine as this is low molecular weight thiol moiety containing compound as mentioned by Brinkley and as successfully used by Marburg to cap the outer layer of the membrane protein conjugate. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of

success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 398-402, 404-408, 410-414 and 416 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 384-396 of copending Application No. 10/583,464 in view of Shimizu, Journal of Neuroscience Research, 70, 451-461.

In the instant invention, applicants claim conjugate comprising a peptide immunogen/polypeptide carrier conjugate wherein the peptide immunogen comprising a Aβ peptide or fragment or analog thereof and wherein the derivatized polypeptide functional group is capped thereby the carrier polypeptide retains the immune response functionality against the peptide conjugate that would otherwise not occur without the carrier.

Claims of copending Application No. 10/583,464 are drawn to peptide immunogen/polypeptide conjugate in general. Claims of copending Application No. 10/583,464 are not drawn to conjugate comprising Aβ peptide as the immunogen peptide.

Shimizu discloses the conjugate of KLH with Aβ1-12 peptide that comprises the fragment of instantly elected SEQ ID NO:2 (page 452, column 2). Since the conjugate of Shimizu were administered to rabbits, it comprises of pharmaceutically acceptable.

One of ordinary skill in the art would combined the teachings of copending Application No. 10/583,464 and Shimizu to arrive at the instant invention since Shimizu discloses the conjugates of Aβ peptide conjugated to carrier protein KLH. One of ordinary skill the art would have been motivated to do so given the fact that Shimizu successfully raised antibodies against

the Aβ peptide-KLH conjugate. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

This is a provisional obviousness-type double patenting rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SATYANARAYANA R. GUDIBANDE/
Examiner, Art Unit 1654

/Andrew D Kosar/
Primary Examiner, Art Unit 1654